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UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE BOARD OF PATENT APPEALS
AND INTERFERENCES

Ex parte EDWIN SOUTHERN

Appeal 2009-010829[1]
Application 10/772,467[2]
Technology Center 1600

Decided: June 2, 2010[3]

Before LORA M. GREEN, FRANCISCO C. PRATS, and
JEFFREY N. FREDMAN *Administrative Patent Judges*.

PRATS, *Administrative Patent Judge*.

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[1] Oxford Gene Technology Limited is the real party in interest (App. Br. 3).
[2] This application has a significant and lengthy parentage, with priority claims dating back to 1988 (App. Br. 4).

In particular, this application is a divisional of Ser. No. 09/422,803, now abandoned, which is a divisional of Ser. No. 08/925,676, now U.S. Patent No. 6,054,270, which in turn is a divisional of Ser. No. 08/230,012, now U.S. Patent. No. 5,700,637 (*id.*).

The Appeal Brief states that both the '270 and '637 patents have been involved in reexamination proceedings and infringement litigation (*id.* at 4-5).

[3] Oral argument was presented in this case on May 13, 2010.

DECISION ON APPEAL

This appeal under 35 U.S.C. § 134 involves claims to an apparatus for analyzing polynucleotides. The Examiner rejected the claims as obvious.

We have jurisdiction under 35 U.S.C. § 6(b). We affirm-in-part.

STATEMENT OF THE CASE

Claims 17-27, 86, and 87 stand rejected and are on appeal (App. Br. 6).[4] Claim 17 is representative and reads as follows:

> Claim 17. Apparatus for analysing a polynucleotide, the apparatus comprising: a support having an impermeable surface; porous material attached to the impermeable surface; and an array of oligonucleotides with predetermined sequences attached to the porous material, wherein the array comprises at least two defined cells, the sequence of the oligonucleotides of a first cell is different from the sequence of the oligonucleotides of a second cell, and the oligonucleotides are shorter than the polynucleotide.

The sole rejection before us for review is the Examiner's rejection of claims 17-27, 86, and 87 under 35 U.S.C. § 103(a) as being unpatentable over Stavrianopoulos[5] and Matkovich[6] (Ans. 5-7).

OBVIOUSNESS

ISSUE

The Examiner cites Stavrianopoulos as disclosing an impermeable substrate-bound array of oligonucleotides having predetermined sequences (Ans. 5). To meet the claims' requirement of a porous material attached to the impermeable surface, the Examiner cites Matkovich as disclosing "the

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[4] Appeal Brief filed September 25, 2008.
[5] U.S. Patent No. 4,994,373 (filed Jul. 20, 1989).
[6] U.S. Patent No. 4,828,386 (filed Jun. 19, 1987).

use of a microporous membrane on top of a support . . . which can be used to bind biologically active substances including nucleic acids" (*id.* at 6-7).

Based on the references' teachings, the Examiner concludes that an ordinary artisan would have considered it obvious "to modify the apparatus taught by Stavrianopoulos et al. to insert a porous membrane with covalently attached oligonucleotides, as taught by Matkovich" (*id.* at 7). The Examiner reasons that an artisan would have been prompted to make this modification "because Matkovich et al. teach that a porous surface results in a better binding capacity of biological substances" (*id.*).

Appellant contends that the Examiner erred in finding that an ordinary artisan would have combined the two references because Stavrianopoulos is directed to nucleic acid assays, whereas Matkovich is concerned with antibody binding, and the references are therefore nonanalogous art (App. Br. 12). Moreover, Appellant argues, Stavrianopoulos teaches that porous materials are less desirable when practicing the invention described therein (*id.* at 13).

Appellant further contends that the Examiner erred in finding that Stavrianopoulos meets the requirement in claim 17 that the arrayed oligonucleotides have "predetermined sequences" because the reasons for allowance in one of patented divisional parent cases interpreted that language as requiring that "'the complete sequence of each and every oligonucleotide probe on the array surface is known'" (*id.* at 14 (italicization omitted)). Appellant contends that this interpretation is consistent with the teachings in the Specification (*id.* at 15-16). In contrast, Appellant argues, Stavrianopoulos' methods involve attaching oligonucleotides of unknown sequence to the substrate (*id.* at 15).

Appellant further argues that the Examiner erred in finding that Stavrianopoulos meets claim 17's requirement that the array includes "'at least two defined cells, [in which] the sequence of the oligonucleotides of a first cell is different from the sequence of the oligonucleotides of a second cell'" (*id.* at 16).

Appellant argues further that the Examiner erred in concluding that the cited references teach or suggest the limitations requiring covalent attachment of the oligonucleotide to the porous substrate (claims 23 and 86), attachment by a terminal nucleotide (claims 24 and 87), and in situ attachment of the oligonucleotides (claim 25) (App. Br. 17-21).

In view of the positions advanced by Appellant and the Examiner, the issue with respect to this rejection is whether the Examiner's conclusion of obviousness is supported by the evidence of record.

FINDINGS OF FACT ("FF")

Stavrianopoulos

1. Stavrianopoulos discloses "a method for quantifiably detecting a targeted polynucleotide sequence in a sample of biological and/or nonbiological material employing a probe capable of generating a soluble signal" (Stavrianopoulos, col. 1, ll. 15-18).

2. In Stavrianopoulos' method, "[an] analyte [which] may be a DNA or RNA molecule of small or high molecular weight" (*id.* at col. 1, ll. 29-30) from a biological sample is "preferably denatured into single-stranded form, and then directly fixed to a suitable solid support" (*id.* at col. 5, ll. 37-39).

3. Thus, "[f]or example, glass plates provided with an array of depressions or wells would have samples of the various denatured analytes

deposited therein, the single-stranded analytes being fixed to the surfaces of the wells" (*id.* at col. 8, ll. 41-45).

4. To determine whether the immobilized nucleic acid from the biological samples includes a particular sequence of interest, "polynucleotide probes provided with a chemical label may be deposited in each of the wells for hybridization to any complementary single-stranded analyte therein. After washing to remove any non-hybridized probe, the presence of any hybrid probe-analyte is then detectable" (*id.* at col. 8, ll. 45-50).

5. Stavrianopoulos discloses:

> It is preferred that the solid support to which the analyte is fixed be non-porous and transparent, such as glass, or alternatively, plastic, polystyrene, polyethylene, dextran, polypropylene and the like. Conventional porous materials, e.g., nitrocellulose filters, although less desirable for practice of the method of the present invention, may also be employed as a support.

(*Id.* at col. 5, ll. 46-52.)

6. Stavrianopoulos discloses an example in which phage lambda DNA is used as the analyte, with alkaline phosphatase/paranitrophenylphosphate as the signaling moiety (*see id.*, *e.g.*, at col. 9, ll. 51-55), as well as an example using adenovirus 2 DNA as the analyte (*id.* at col. 11, ll. 20-35).

7. Stavrianopoulos discloses that a technique useful for immobilizing the sample nucleic acids involves functionalizing the glass substrate such that the "treated glass surface will . . . have available alkylamine thereon suitable for immobilizing or fixing any negatively charged polyelectrolytes applied thereto" (*id.* at col. 8, ll. 32-35).

8. Stavrianopoulos discloses that its invention "also encompasses indirect fixation of the analyte, such as in situ techniques where the cell is fixed to the support" (*id.* at col. 5, ll. 41-43).

Matkovich

9. Matkovich discloses a "multiwell plate . . . showing superior characteristics in binding antibody and other substances of biological origin" (Matkovich, col. 3, ll. 3-7).

10. Matkovich discloses that "[s]uperior capacity for the binding of biological substances is obtained by providing a unitary insert comprising a biochemically compatible microporous surface capable of binding antibody and/or other substances of interest for carrying out binding assays that is shaped to fit into at least one well of the plate" (*id.* at col. 3, ll. 13-19).

11. Matkovich discloses that its methods can involve the "use of a backing material to support the microporous surface (the backing material being either rigid or flexible, porous or non-porous)" (*id.* at col. 3, ll. 24-27).

12. Matkovich discloses that the "reactant, which may be of ionic, molecular, or macromolecular nature, may be immobilized on the reaction layer by strong physical forces or by being bonded in some manner, such as covalent chemical coupling, to the surface of the reaction layer" (*id.* at col. 4, l. 64, through col. 5, l. 1).

13. Matkovich discloses:

> Although the bound material is usually an antibody or antigen, any reference herein to a binding surface capable of binding an antibody (or similar language) is not limiting or to be considered as indicating that only an antibody can be bound to the surface. Specific examples of molecules that participate in

> binding interactions suitable for use in assays of the type described here are set forth later in this specification.

(*Id.* at col. 3, l. 63, through col. 4, l. 2.)

14. Matkovich thus discloses, for example, that the "reagent or acceptor molecule bound directly to the reaction substrate or the ligand being tested for include such substances as immunoglobulins or antibodies, either polyclonal or monoclonal, antigenic substances, apoproteins, receptors, glycoproteins, lectins, carbohydrates, hormones, enzymes, carrier proteins, heparin, coagulation factors, enzyme substrates, inhibitors, cofactors, *nucleic acids*, etc." (*id.* at col. 6, ll. 52-60 (emphasis added)).

PRINCIPLES OF LAW

In *KSR Int' l Co. v. Teleflex Inc.*, 550 U.S. 398, 415 (2007), the Supreme Court emphasized "an expansive and flexible approach" to the obviousness question, and in particular noted that the analysis "need not seek out precise teachings directed to the specific subject matter of the challenged claim, for a court can take account of the inferences and creative steps that a person of ordinary skill in the art would employ." *Id.* at 418; *see also id.* at 421 ("A person of ordinary skill is . . . a person of ordinary creativity, not an automaton.").

The Court also advised that "if a technique has been used to improve one device, and a person of ordinary skill in the art would recognize that it would improve similar devices in the same way, using the technique is obvious unless its actual application is beyond his or her skill. *Id.* at 418.

Regarding claim interpretation, during examination the PTO must interpret terms in a claim using "the broadest reasonable meaning of the words in their ordinary usage as they would be understood by one of

ordinary skill in the art, taking into account whatever enlightenment by way of definitions or otherwise that may be afforded by the written description contained in the applicant's specification." *In re Morris*, 127 F.3d 1048, 1054 (Fed. Cir. 1997).

ANALYSIS

Claim 17

We are not persuaded that the Examiner erred in concluding that an ordinary artisan would have considered claim 17 obvious in view of the cited references.

Claim 17 recites an apparatus for analyzing a polynucleotide. The apparatus has a support with an impermeable surface, and a porous material attached to the impermeable surface.

The apparatus of claim 17 also has an array of oligonucleotides attached to the porous material. The array comprises at least two defined cells, with the sequence of the oligonucleotides of a first cell being different from the sequence of the oligonucleotides of a second cell.

Claim 17 recites that the "oligonucleotides [attached to the porous surface] are shorter than the polynucleotide" analyzed by the apparatus. As this feature is directed to the method by which the apparatus is used, we conclude that it places essentially no structural limitation on the apparatus of claim 17.

Claim 17 also recites that the oligonucleotides attached to the porous surface have "predetermined sequences." Appellant urges that this limitation requires a practitioner to know the complete sequence of each and every oligonucleotide attached to the apparatus (App. Br. 14).

Even if we adopt this interpretation, however, a porous substrate having two different oligonucleotides attached to it has the same structure whether or not the practitioner knows the exact sequence of those oligonucleotides. That is, the practitioner's knowledge in no way affects the actual structure of the array. The use of "predetermined" is an attempt to incorporate a required process step into this product claim. We therefore conclude that the recitation "predetermined sequences" in claim 17 does not place any structural limitation on the claimed apparatus.

Accordingly, we interpret claim 17 as encompassing an apparatus composed of an impermeable substrate with a porous material attached to it, the porous material having two or more different oligonucleotides attached to it, the different oligonucleotides being present in distinct defined cells.

We agree with the Examiner that the cited references suggest an apparatus that has these features.

As noted above, Stavrianopoulos discloses that "glass plates provided with an array of depressions or wells would have samples of the various denatured analytes deposited therein, the single-stranded analytes being fixed to the surfaces of the wells" (Stavrianopoulos, col. 8, ll. 41-45 (FF 3)). We agree with the Examiner that this disclosure at the very least suggests claim 17's requirement of an array with at least two different oligonucleotides attached to distinct defined cells.

Appellant argues that it is not reasonable to find that Stavrianopoulos meets that feature because

> One reasonable way of using the Stavrianopoulos assay in a multiwell format would be to add the same analyte to separate wells and then to add a different probe to each well. Thus each well reveals whether a particular sequence is present <u>in a single</u>

> analyte. For instance, a single patient's blood could be screened for a dozen different mutations. In this format there are "various denatured analytes" but each analyte is identical, whereas claim 17 requires that "*the sequence of the oligonucleotides of a first cell is different from the sequence of the oligonucleotides of a second cell*".

(Reply Br. 3.)

We are not persuaded by this argument. While it might be reasonable to interpret Stavrianopoulos in the manner Appellant posits, we agree with the Examiner that an ordinary artisan would have considered it at least equally reasonable to interpret the disclosure of applying "various denatured analytes" to an array of depressions or wells as suggesting that oligonucleotides from different biological samples should be applied to the different wells. Doing so would allow the various samples to be tested with a single probe to determine if the samples, for example from different individuals being tested, contained a particular nucleic acid sequence of interest.

Accordingly, we are not persuaded that the Examiner erred in finding that Stavrianopoulos teaches or suggests the requirement in claim 17 that the array have two or more defined cells that contain oligonucleotides with different sequences. Moreover, as discussed above, claim 17's requirement that the sequences be "predetermined" does not place any structural limitation on the apparatus, and we are therefore not persuaded that the array described by Stavrianopoulos is distinguishable from the array recited in claim 17 on that basis.

We are also not persuaded that the cited references fail to suggest adding a porous substrate to Stavrianopoulos' apparatus for attachment of

the oligonucleotides. Specifically, while Stavrianopoulos discloses that it is "preferred that the solid support to which the analyte is fixed be non-porous and transparent" (Stavrianopoulos, col. 5, ll. 46-48 (FF 5)), Stavrianopoulos specifically states that "[c]onventional porous materials, e.g., nitrocellulose filters, although less desirable for practice of the method of the present invention, *may also be employed as a support*" (*id.* at col. 5, ll. 49-52 (FF 5)(emphasis added)).

Moreover, Matkovich discloses that, in assays involving binding of substances contained in biological samples to immobilized molecules, the use of a microporous immobilization substrate provides "[s]uperior capacity for the binding of biological substances" (Matkovich col. 3, ll. 13-14 (FF 10)).

It may be true, as Appellant argues (App. Br. 12), that Matkovich focuses on using the microporous support for attaching antibodies. However, Matkovich explicitly states that its teachings are not limited to antibodies, but instead are applicable to other "molecules that participate in binding interactions" (Matkovich, col. 3, l. 68 through col. 4, l. 1 (FF 13)), including "nucleic acids" (*id.* at col. 6, l. 60 (FF 14)).

Given the references' teachings, we are not persuaded that the Examiner erred in finding that an ordinary artisan would have prompted to use a porous material as the oligonucleotide-immobilizing matrix on Stavrianopoulos' apparatus. For the reasons discussed above, we are not persuaded that the Examiner otherwise erred in concluding that the apparatus suggested by Stavrianopoulos and Matkovich would have been obvious to an ordinary artisan.

We therefore affirm the Examiner's obviousness rejection of claim 17, as well as the rejection of claims, 18-22, 26 and 27, which were not argued separately. *See* 37 C.F.R. § 41.37(c)(1)(vii).

Claim 23

Claim 23 recites the "[a]pparatus of claim 17, wherein the oligonucleotides are covalently attached to the porous material." Appellant contends that Stavrianopoulos and Matkovich do not teach or suggest this limitation because Stavrianopoulos immobilizes oligonucleotides to its substrate by ionic interaction (App. Br. 18).

Thus, Appellant argues, the Examiner has not provided a "reasonable justification why a skilled person who looked to Matkovich would reject Stavrianopoulos'[] choice of charged surfaces for and would instead use covalent bonding" (*id.*). Moreover, Appellant urges, a "person of ordinary skill would not arbitrarily select covalent attachment chemistry for an analyte that is intrinsically ionic in nature and that had been deliberately immobilized by Stavrianopoulos in a non-covalent manner" (*id.*).

We are not persuaded. We note that Stavrianopoulos functionalizes its substrate to provide it with a positive charge that allows immobilization of the negatively charged nucleic acids via ionic interaction (FF 7), which undisputedly does not meet claim 23's requirement of covalent attachment.

As discussed above, however, we agree with the Examiner that an ordinary artisan would have been prompted by the references to use Matkovich's porous material as the oligonucleotide-immobilizing matrix on Stavrianopoulos' apparatus. We further agree with the Examiner that an ordinary artisan using Matkovich's porous material as an oligonucleotide-

immobilizing matrix would have looked to Matkovich to determine suitable methods of attaching substances to its porous material.

As noted above, Matkovich explicitly states that "covalent chemical coupling" was a suitable method for attaching the immobilized reactants to the porous matrix (Matkovich, col. 4, l. 68 (FF 12)). Accordingly, we are not persuaded that an ordinary artisan would have covalently attached the oligonucleotides to Matkovich's porous substrate only through hindsight reasoning, since an ordinary artisan following Matkovich's explicit teaching in that regard would have been advised of the suitability of covalent attachment.

As we agree with the Examiner that the cited references suggest the covalent attachment recited in claim 23, we affirm the Examiner's obviousness rejection of that claim, as well as claim 86, which was argued in the same grouping. *See* 37 C.F.R. § 41.37(c)(1)(vii).

Claim 24

Claim 24 recites the "[a]pparatus of claim [17], wherein the oligonucleotides are covalently attached by a terminal nucleotide."

Appellant contends that the cited references lack disclosures regarding this feature that are specific enough to render the claim obvious (App. Br. 20). The Examiner responds that, while Stavrianopoulos "does not explicitly teach attachment via a terminal nucleotide, the Examiner maintains that Stavrianopoulos et al. suggests such an attachment where he teaches that oligonucleotides are attached such that they can still hybridize. This teaching encompasses attachment via a terminal nucleotide. Matkovich et al. teaches covalent attachment" (Ans. 14).

We find that Appellant has the better position here. In contrast to the situation above, where the prior art explicitly taught the suitability of covalent attachment, in the instant case the Examiner points to no specific teaching in either reference suggesting that attachment by the terminal nucleotide would be suitable in, or even achievable by, the disclosed methods. Thus, while we acknowledge Stavrianopoulos' teaching regarding the desirability of immobilizing the oligonucleotides in a manner that allows hybridization to a probe, the Examiner has not provided evidence suggesting that adequate hybridization was unattainable using the attachment methods described in the references, nor has the Examiner pointed to any specific evidence that of record suggesting that attachment of oligonucleotides through the terminal nucleotide would have been desirable, or even suitable, in the methods of Stavrianopoulos and Matkovich.

Accordingly, we reverse the Examiner's obviousness rejection of claim 24, as well as claim 87, which also requires the oligonucleotides to be attached by a terminal nucleotide.

Claim 25

Claim 25 recites the "[a]pparatus of claim 17, wherein the oligonucleotides are synthesized *in situ*."

To meet that limitation the Examiner cites Stavrianopoulos' disclosure that its invention "also encompasses indirect fixation of the analyte, such as in situ techniques where the cell is fixed to the support" (Stavrianopoulos, col. 5, ll. 41-43 (FF 8)). Appellant contends that the cited portion of Stavrianopoulos does not relate to in situ synthesis of the actual

oligonucleotides, but instead relates to direct immobilization of the cell containing the target oligonucleotide to the substrate (App. 21).

We agree with Appellant that the cited references do not teach or suggest the apparatus recited in claim 25.

While we interpret claim 25 as a product-by-process claim, we note the Specification's disclosure that in situ synthesis of oligonucleotides begins with the initial covalent attachment of a terminal nucleotide to the substrate via a long aliphatic linker, after which reaction mixtures adding the desired nucleotides via phosphoramidite chemistry are sequentially applied to the covalently linked terminal nucleotide (Spec. 14-16). Thus, viewing the claim in light of the Specification, the in situ synthesis method recited in claim 25 essentially requires the claimed apparatus to have a terminal nucleotide covalently attached to the substrate.

As noted above, we do not agree with the Examiner that the cited references render obvious apparatuses in which the oligonucleotides are attached to the porous substrate by one of the oligonucleotides' terminal nucleotides. Nor are we persuaded that Stavrianopoulos' disclosure of attaching cells containing the oligonucleotides, rather than the oligonucleotides themselves, suggests the structure required in claim 25.

Accordingly, we reverse the Examiner's obviousness rejection of claim 25.

SUMMARY

We affirm the Examiner's rejection of claims 17-23, 26, 27, and 86, under 35 U.S.C. § 103(a) as being obvious in view of Stavrianopoulos and Matkovich.

However, we reverse the Examiner's rejection of claims 24, 25, and 87 over those references.

TIME PERIOD

No time period for taking any subsequent action in connection with this appeal may be extended under 37 C.F.R. § 1.136(a).

AFFIRMED-IN-PART

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